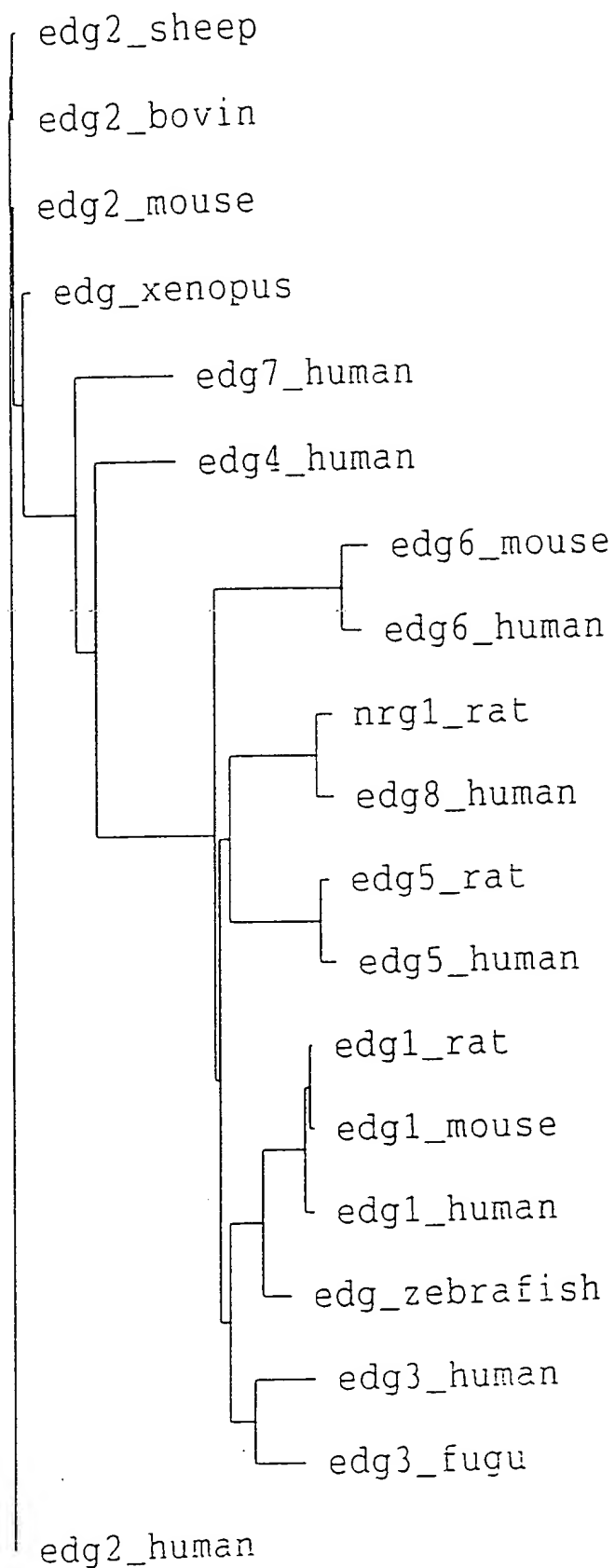FIG 1A:

```
   1 ATGGAGTCGGGGCTGCTGCGGCCGGCGCCGGTGAGCGAGGTCATCGTCCTGCATTACAAC
     M  E  S  G  L  L  R  P  A  P  V  S  E  V  I  V  L  H  Y  N

  61 TACACCGGCAAGCTCCGCGGTGCGCGCTACCAGCCGGGTGCCGGCCTGCGCGCCGACGCC
     Y  T  G  K  L  R  G  A  R  Y  Q  P  G  A  G  L  R  A  D  A

 121 GTGGTGTGCCTGGCGGTGTGCGCCTTCATCGTGCTAGAGAATCTAGCCGTGTTGTTGGTG
     V  V  C  L  A  V  C  A  F  I  V  L  E  N  L  A  V  L  L  V

 181 CTCGGACGCCACCCGCGCTTCCACGCTCCCATGTTCCTGCTCCTGGGCAGCCTCACGTTG
     L  G  R  H  P  R  F  H  A  P  M  F  L  L  L  G  S  L  T  L

 241 TCGGATCTGCTGGCAGGCGCCGCCTACGCCGCCAACATCCTACTGTCGGGGCCGCTCACG
     S  D  L  L  A  G  A  A  Y  A  A  N  I  L  L  S  G  P  L  T

 301 CTGAAACTGTCCCCCGCGCTCTGGTTCGCACGGGAGGGAGGCGTCTTCGTGGCACTCACT
     L  K  L  S  P  A  L  W  F  A  R  E  G  G  V  F  V  A  L  T

 361 GCGTCCGTGCTGAGCCTCCTGGCCATCGCGCTGGAGCGCAGCCTCACCATGGCGCGCAGG
     A  S  V  L  S  L  L  A  I  A  L  E  R  S  L  T  M  A  R  R

 421 GGGCCCGCGCCCGTCTCCAGTCGGGGGCGCACGCTGGCGATGGCAGCCGCGGCCTGGGGC
     G  P  A  P  V  S  S  R  G  R  T  L  A  M  A  A  A  A  W  G

 481 GTGTCGCTGCTCCTCGGGCTCCTGCCAGCGCTGGGCTGGAATTGCCTGGGTCGCCTGGAC
     V  S  L  L  L  G  L  L  P  A  L  G  W  N  C  L  G  R  L  D

 541 GCTTGCTCCACTGTCTTGCCGCTCTACGCCAAGGCCTACGTGCTCTTCTGCGTGCTCGCC
     A  C  S  T  V  L  P  L  Y  A  K  A  Y  V  L  F  C  V  L  A

 601 TTCGTGGGCATCCTGGCCGCTATCTGTGCACTCTACGCGCGCATCTACTGCCAGGTACGC
     F  V  G  I  L  A  A  I  C  A  L  Y  A  R  I  Y  C  Q  V  R

 661 GCCAACGCGCGGCGCCTGCCGGCACGGCCCGGGACTGCGGGGACCACCTCGACCCGGGCG
     A  N  A  R  R  L  P  A  R  P  G  T  A  G  T  T  S  T  R  A

 721 CGTCGCAAGCCGCGCTCGCTGGCCTTGCTGCGCACGCTCAGCGTGGTGCTCCTGGCCTTT
     R  R  K  P  R  S  L  A  L  L  R  T  L  S  V  V  L  L  A  F

 781 GTGGCATGTTGGGGCCCCCTCTTCCTGCTGCTGTTGCTCGACGTGGCGTGCCCGGCGCGC
     V  A  C  W  G  P  L  F  L  L  L  L  L  D  V  A  C  P  A  R

 841 ACCTGTCCTGTACTCCTGCAGGCCGATCCCTTCCTGGGACTGGCCATGGCCAACTCACTT
     T  C  P  V  L  L  Q  A  D  P  F  L  G  L  A  M  A  N  S  L

 901 CTGAACCCCATCATCTACACGCTCACCAACCGCGACCTGCGCCACGCGCTCCTGCGCCTG
     L  N  P  I  I  Y  T  L  T  N  R  D  L  R  H  A  L  L  R  L

 961 GTCTGCTGCGGACGCCACTCCTGCGGCAGAGACCCGAGTGGCTCCCAGCAGTCGGCGAGC
     V  C  C  G  R  H  S  C  G  R  D  P  S  G  S  Q  Q  S  A  S

1021 GCGGCTGAGGCTTCCGGGGGGCCTGCGCCGCTGCCTGCCCCCGGGCCTTGATGGGAGCTTC
     A  A  E  A  S  G  G  L  R  R  C  L  P  P  G  L  D  G  S  F

1081 AGCGGCTCGGAGCGCTCATCGCCCCAGCGCGACGGGCTGGACACCAGCGGCTCCACAGGC
     S  G  S  E  R  S  S  P  Q  R  D  G  L  D  T  S  G  S  T  G
1141 AGCCCCGGTGCACCCACAGCCGCCCGGACTCTGGTATCAGAACCGGCTGCAGACTGA
     S  P  G  A  P  T  A  A  R  T  L  V  S  E  P  A  A  D  *
```

FIG 1B

edg2_sheep

edg2_bovin

edg2_mouse

edg_xenopus

edg7_human

edg4_human

edg6_mouse

edg6_human

nrg1_rat

edg8_human

edg5_rat

edg5_human

edg1_rat

edg1_mouse

edg1_human

edg_zebrafish

edg3_human

edg3_fugu

edg2_human

Fig. 1C

```
           1                                                                    60
edg2_human MAAISTSIPV ISQPQFTAMN EPQCFYNESI AFFYNRSGKH LAT.EWNTVS KLVQGL..GI
edg7_human ---------- -------MNXE..CHYDKHM DFFYNRSNTD TVD.OW.TGT KLVIVLCVGT
edg4_human ---------- -------MVI NGQCYYNETI GFFYNNSGKE LSS.HWR..P KDVTVVALGL
edg1_human -----MGPTS VPLVKAHRSS VSDYVNYDII VRHYNYTGKL ..NISADKEN SIKLTSVVFI
edg3_human ---------- --MATALPPR LQPVRGNETL REHYQYVGKL AGRLKEASEG S.TITTVLFL
edg5_human ---------- ------MGSL YSEYLNPNKV QEHYNYTKE. ..TLETQETT SRQYASAFIV
edg8_human ---------- -----MESGL LRPAPVSEVI VLHYNYTGKL RG.ARYQPGA GLRADAVVCL
edg6_human -----MNATG TPVAPESCQQ LAAGGHSRLI VLHYNHSGRL AGR.GGPEDG GLGALRGLSV

           61                                                                   120
edg2_human TVCIFIMLAN LLVMVAIYVN RRFHFPIYYL MANLAAADFF AGLAYFYLMF NTGPNTRRLT
edg7_human FFCLFIFFSN SLVIAAVIKN RKFHFPFYYL LANLAAADFF AGIAYVFLMF NTGPVSKTLT
edg4_human TVSVLVLLTN LLVIAAIASN RRFHQPIYYL LGNLAAADLF AGVAYLFLMF HTGPRTARLS
edg1_human LICCFIILEN IFVLLTIWKT KKFHFPMYYL IGNLALSDLL AGVAYTANLL LSGATTYKLT
edg3_human VICSFIVLEN LMVLIAIWKN NKFHNRMYFF IGNLALCDLL AGIAYKVNIL MSGKKTFSLS
edg5_human ILCCAIVVEN LLVLIAVARN SKFHSAMYLF LGNLAASDLL AGVAFVANTL LSGSVTLRLT
edg8_human AVCAFIVLEN LAVLLVLGRH PRFHAPMFLL LGSLTLSDLL AGAAYAANIL LSGPLTLKLS
edg6_human AASCLVVLEN LLVLAAITSH MRSRFWVYYC LVNITLSDLL TGAAYLANVL LSGARTFRLA

           121                                                                  180
edg2_human VSTWLLRQGL IDTSLTASVA NLLAIAIERH ITVFR.MQLH TRMSNRRVVV VIVVIWTMAI
edg7_human VNRWFLRQGL LDSSLTASLT NLLVIAVERH MSIMR.MRVH SNLTKRRVTL LILLVWAIAI
edg4_human LEGWFLRQGL LDTSLTASVA TLLAIAVERH RSVMA.VQLH SRLPRGRVVM LIVGVWVAAI
edg1_human PAQWFLREGS MFVALSASVF SLLAIAIERY ITMLK.MKLH NGSNNFRLFL LISACWVISL
edg3_human PTVWFLREGS MFVALGASTC SLLAIAIERH LTMIK.MRPY DANKRHRVFL LIGMCWLIAF
edg5_human PVQWFAREGS ASITLSASVF SLLAIAIERH VAIAK.VKLY GSDKSCRMLL LIGASWLISL
edg8_human PALWFAREGG VFVALTASVL SLLAIALERS LTMAR.RGPA PVSSRGRTLA MAAAAWGVSL
edg6_human PAQWFLREGL LFTALAASTF SLLFTAGERF ATMVRPVAES GATKTSPVYG FIGLCWLLAA

           181                                                                  240
edg2_human VMGAIPSVGW NCICDIENCS NMAPLYSDSY LVFWAIFNLV TFVVMVVLYA HIFGYVRQRT
edg7_human FMGAVPTLGW NCLCNISACS SLAPIYSRSY LVFWTVSNLM AFLIMVVVYL RIYVYVKRKT
edg4_human GLGLLPAHSW HCLCALDRCS RMAPLLSRSY LAVWALSSLL VFLLMVAVYT RIFFYVRRRV
edg1_human ILGGLPIMGW NCISALSSCS TVLPLYHKHY ILFCTTVFTL LLLSIVILYC RIYSLVRTRS
edg3_human TLGALPILGW NCLHNLPCCS TILPLYSKHY IAFCISIFTA ILVTIVILYA RIYFLVKRSSH
edg5_human VLGGLPILGW NCLGHLEACS TVLPLYAKHY VLFCVTIFSI ILLAIVALYV RIYCVVRSSH
edg8_human LLGLLPALGW NCLGRLDACS TVLPLYAKAY VLFCVLAFVG ILAAICALYA RIYCQVRANA
edg6_human LLGMLPLLGW NCLCAFDRCS SLLPLYSKRY ILFCLVIFAG VLATIMGLYG AIFRLVQASG

           241                                                                  300
edg2_human MRMSRHSSGP R......RNR DTMMSLLKTV VIVLGAFIIC WTPGLVLLLL D.VCCP..QC
edg7_human NVLSPHTSGS I......SRR RTPMKLMKTV MTVLGAFVVC WTPGLVVLLL DGLNCR..QC
edg4_human QRMAEHVSCH P......RYR ETTLSLVKTV VIILGAFVVC WTPGQVVLLL DGLGCE..SC
edg1_human RRLTFR.... .KNISKASRS SENVALLKTV IIVLSVFIAC WAPLFILLLL DV.GCKVKTC
edg3_human RKVANH.... .NN......S ERSMALLRTV VIVVSVFIAC WSPLFILFLI DV.ACRVQAC
edg5_human ADMA......A PQTLALLKTV TIVLGVFIVC WLPAFSILLL DY.ACPVHSC
edg8_human RRLPARPGTA GTTSTRARRK PRSLALLRTL SVVLLAFVAC WGPLFLLLLL DV.ACPARTC
edg6_human QKAP...... ...RPAARRK ARR..LLKTV LMILLAFLVC WGPLFGLLLA DVFGSNLWAQ

           301                                                                  360
edg2_human DVLAYEKFFL LLAEFNSAMN PIIYSYRDKE MSATFRQILC CQRSENPTGP TESSDRSASS
edg7_human GVQHVKKFWL LLALLNSVVN PIIYSYKDED MYGTMKKMIC CFSQENP... ....ERRPSR
edg4_human NVLAVEKYFL LLAEANSLVN AAVYSCRDAE MRRTFRRLLC CACLRQSTRE SVHYTSSACG
edg1_human DILFRAEYFL VLAVLNSGTN PIIYTLTNKE MRRAFIRIMS CCKCPSGD.. .........S
edg3_human PILFKAHYFF AVSTLNSLLN PVIYTWRSRD LRREVLRPLQ CWRPGVGV.. .........G
edg5_human PILYKAHYFF AVSTLNSLLN PVIYTWRSRD LRREVLRPLQ CWRPGVGV.. .........G
edg8_human PVLLQADPFL GLAMANSLLN PIIYTLTNRD LRHALLRLVC CGRHSCGRDP SGS..QQSAS
edg6_human EYLRGMDWIL ALAVLNSAVN PIIYSFRSRE VCRAVLSFLC CGCLRLGMRG PGDCLARAVE

           361                                                                  418
edg2_human LNHTILAGVH SNDHSVV--- ---------- ---------- ---------- --------
edg7_human IPSTVLSRSD TGSQYIEDSI SQGAVCNKST S--------- ---------- --------
edg4_human GASTRIMLPE NGHPLMTPPF SYLELQRYAA SNKSTAPDOL WVLLAQPNCQ Q-------
edg1_human AGKFKRPIIA GMEFSRSK.. .SDNSSHPQK DEGDNPETIM SSGNVNSSS- --------
edg3_human RGARASPIQP ALDPSRSKSS SSNNSSHSPK VKEDLPHTGP SSCIMDKNAA LQNGIFCN
edg5_human GRRVGTPGH HLLPLRSSSS LERGMHMPTS PTFLEGNTVV ---------- --------
edg8_human AAEASGGLRR CLPPGLDGSF SGSERSSPQR CGLDTSGSTG SPGAPTAART LVSEPAAD
edg6_human AHSGASTTDS SLRP.RDSFR GSRSLSFRMR EPLSSISSVR SI-------- --------
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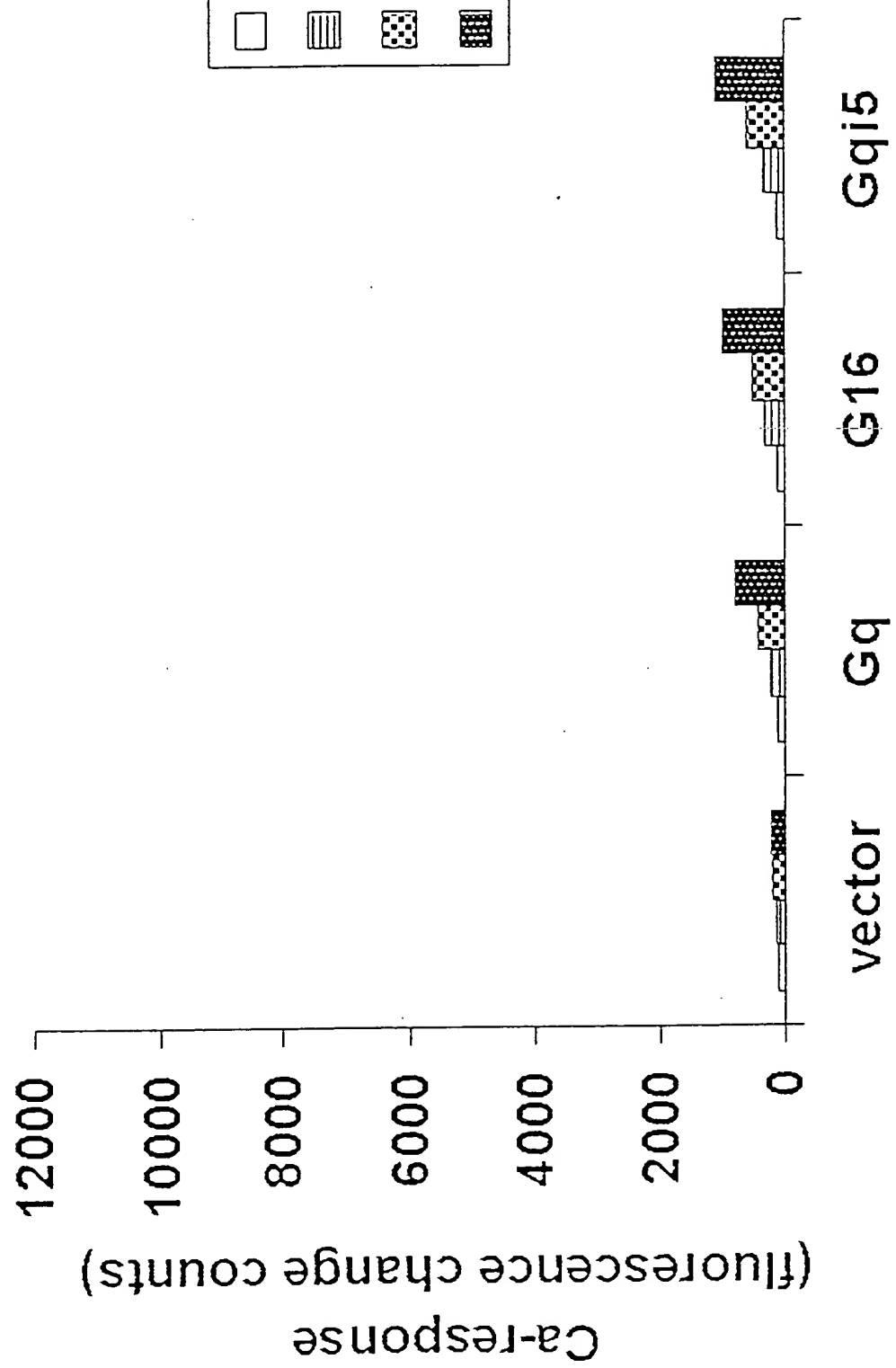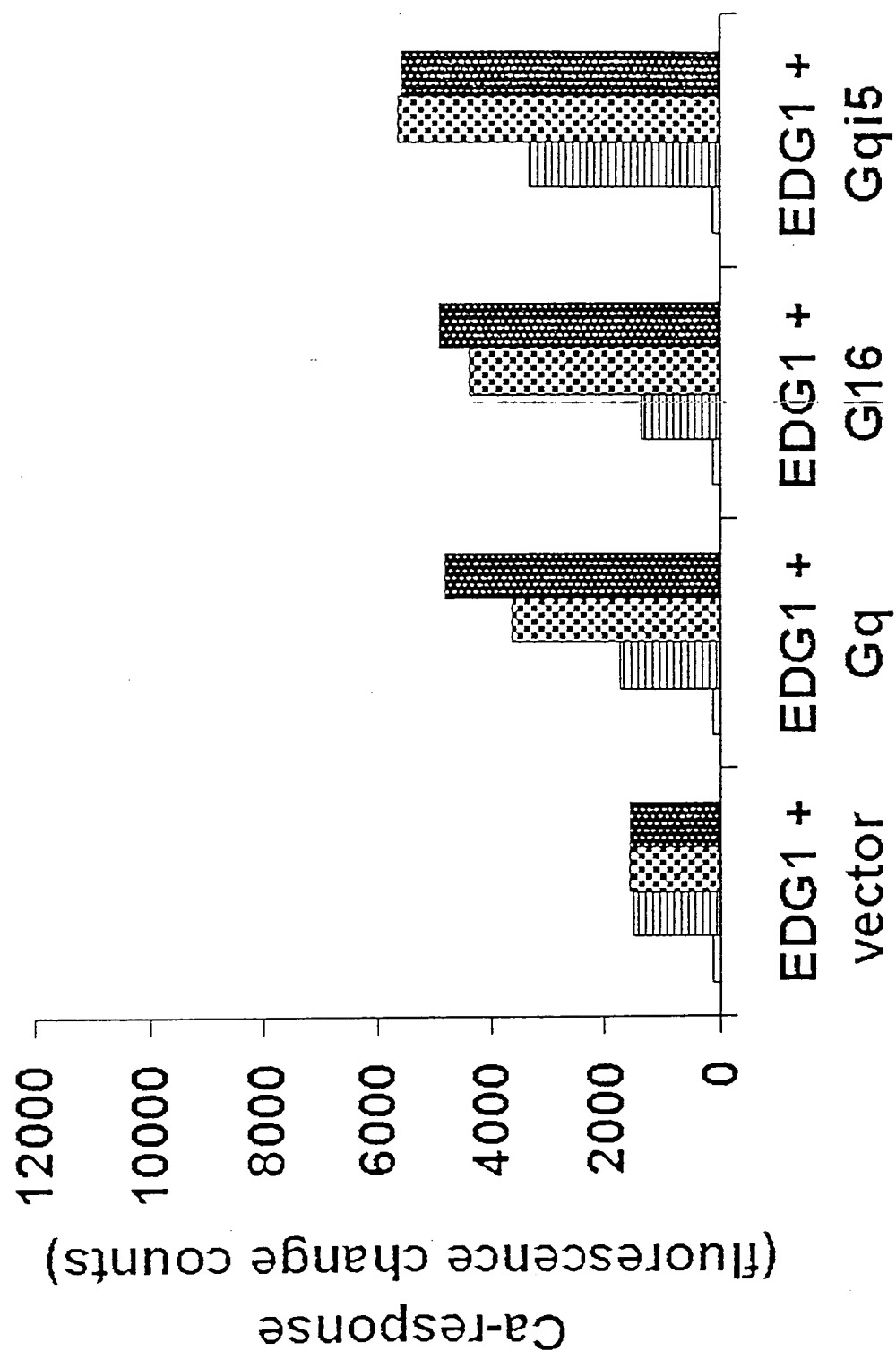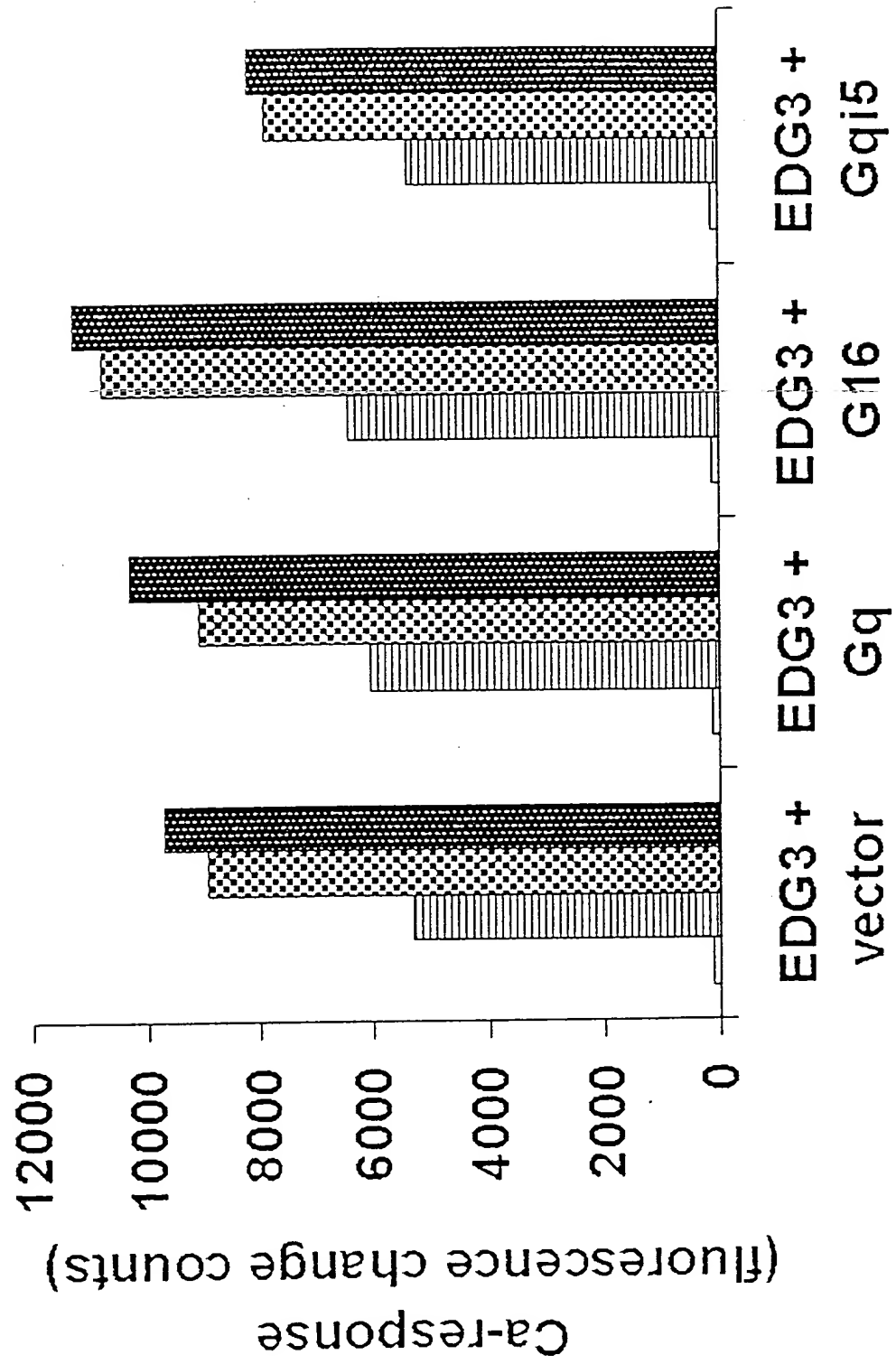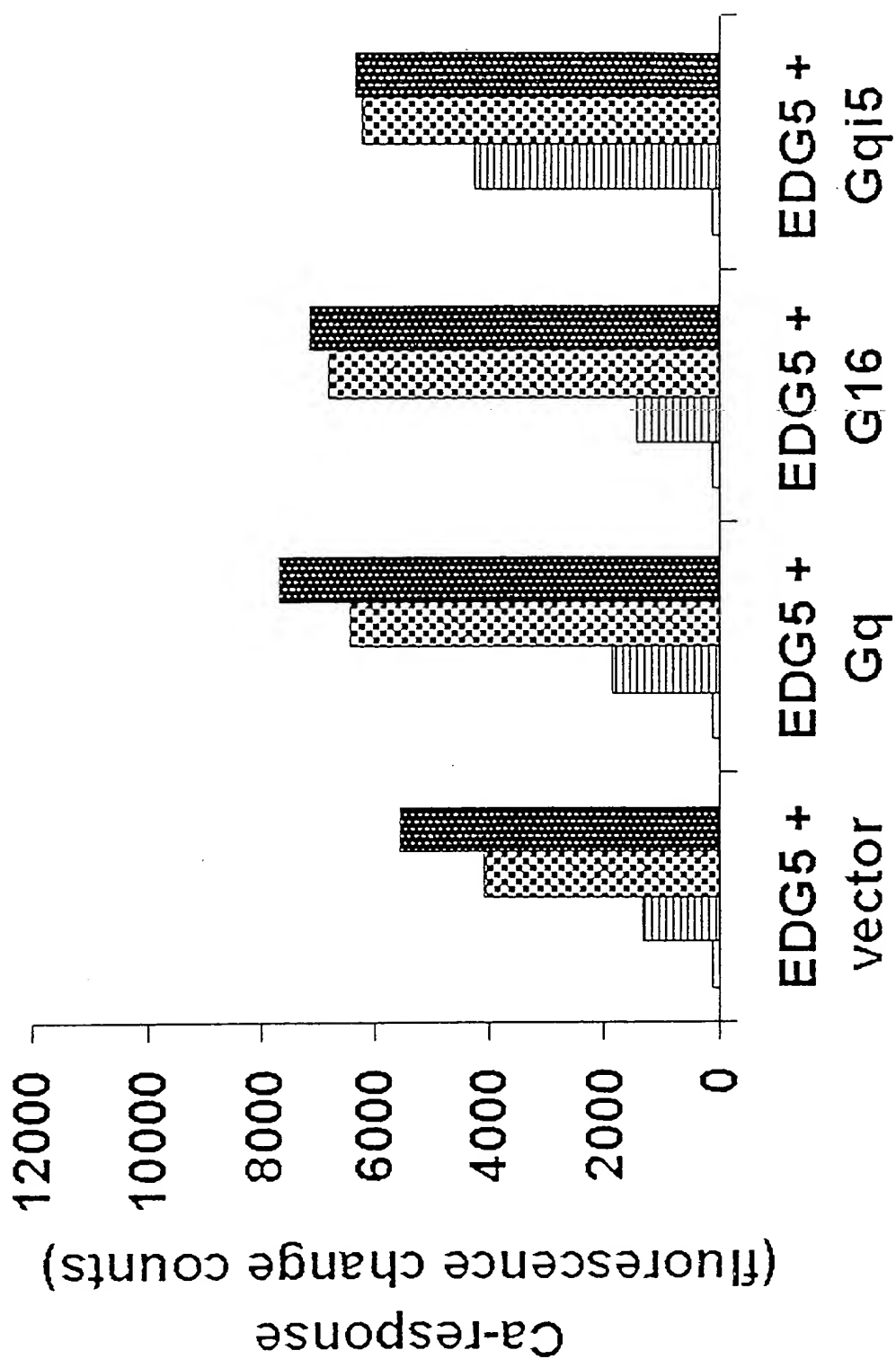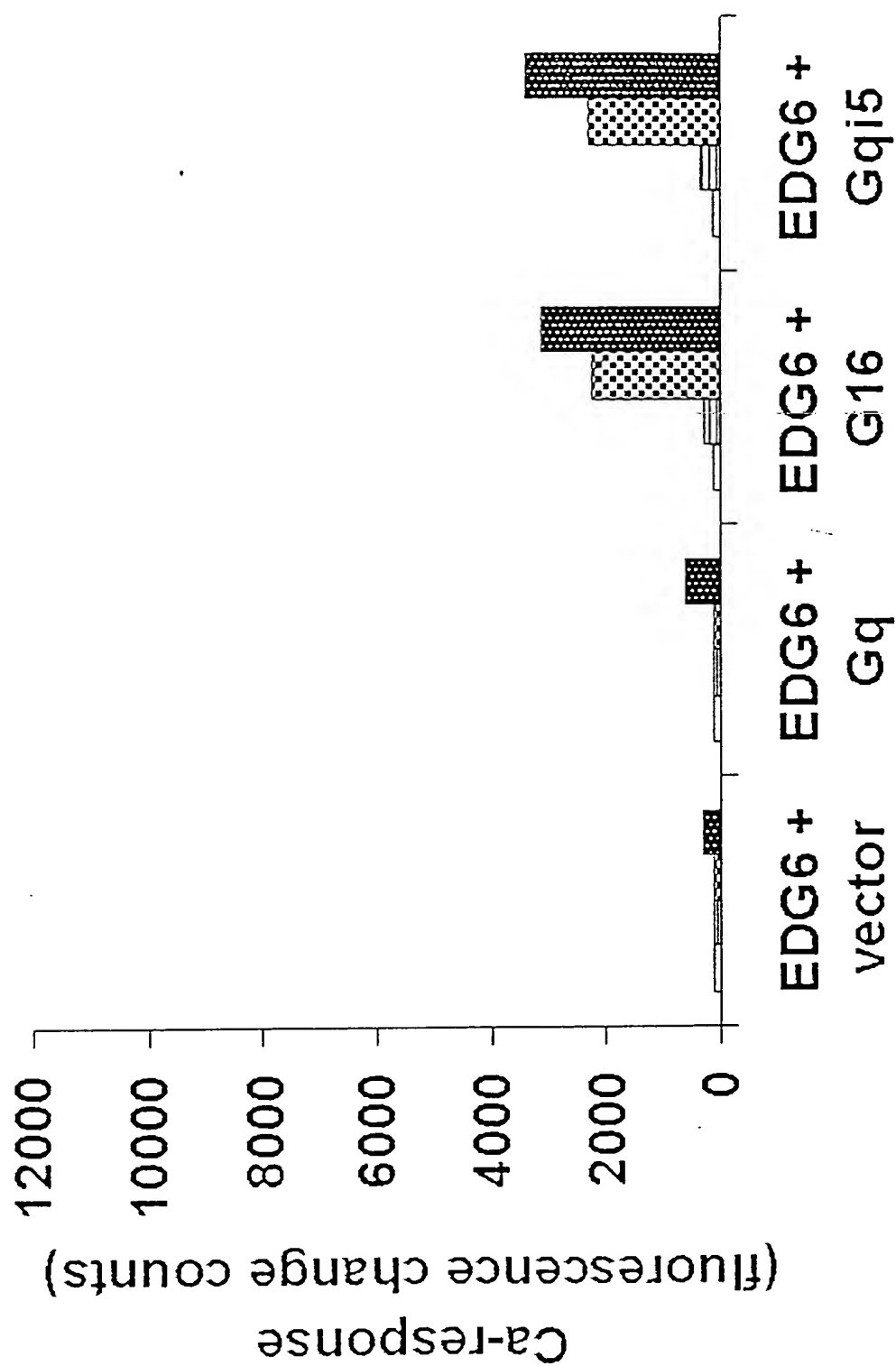
FIG 2A

FIG. 2A: Ca-response (fluorescence change counts) for vector, Gq, G16, and Gqi5 at 0 nM, 10 nM, 100 nM, and 1000 nM.

FIG 2B

Ca-response (fluorescence change counts)

EDG1 + vector   EDG1 + Gq   EDG1 + G16   EDG1 + Gqi5

FIG 2C

Ca-response
(fluorescence change counts)

EDG3 +
vector

EDG3 +
Gq

EDG3 +
G16

EDG3 +
Gqi5

FIG 2D

Ca-response
(fluorescence change counts)

EDG5 +
vector

EDG5 +
Gq

EDG5 +
G16

EDG5 +
Gqi5

0
2000
4000
6000
8000
10000
12000

FIG 2E

Ligand: Os25478Ga

FIG 2F

Ca-response
(fluorescence change counts)

12000
10000
8000
6000
4000
2000
0

EDG8 +
vector

EDG8 +
Gq

EDG8 +
G16

EDG8 +
Gqi5

FIG 3

FIG 4

Human EDG8 tissue expression

5,5 kb
2,4 kb
ßActin

- brain
- heart
- skeletal muscle
- colon (no mucosa)
- thymus
- spleen
- kidney
- liver
- small intestine
- placenta
- lung
- peripheral blood leukocytes

FIG 5A

522 bp

Pos. control
neg. control
HUVECS
HCAEC
HMVEC-L
HPAEC

FIG 5B

522 bp ➡

EDG- 1 2 3 4 5 6 7 8 H₂O
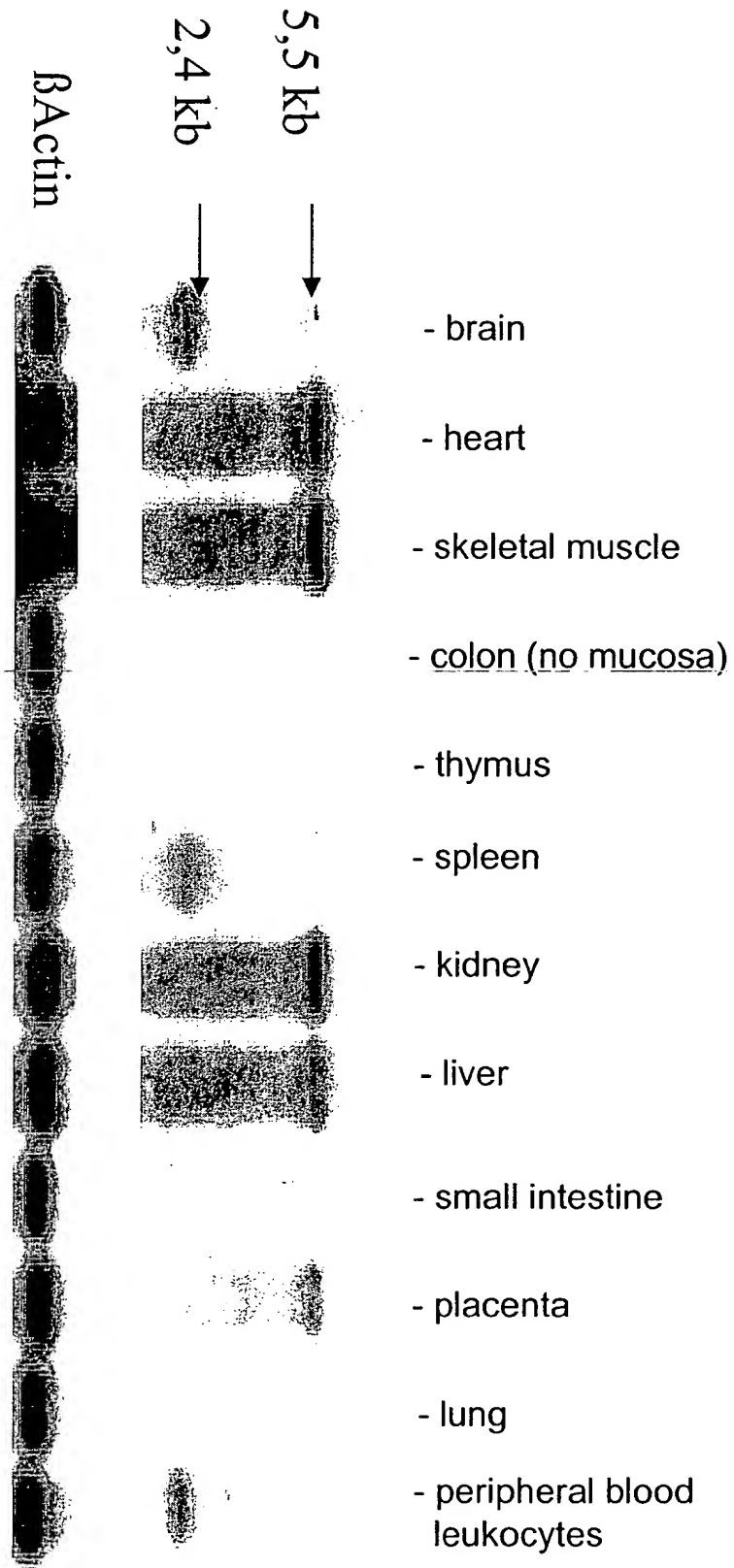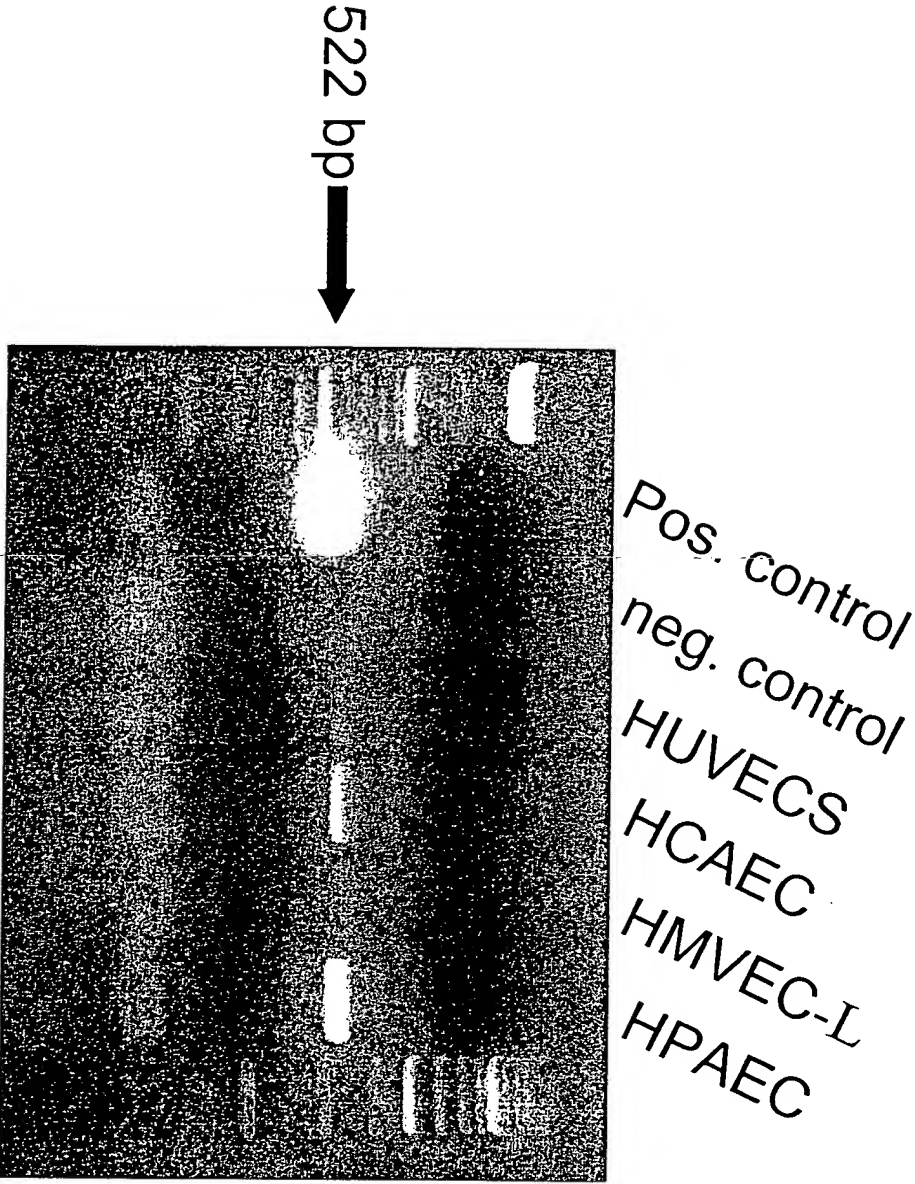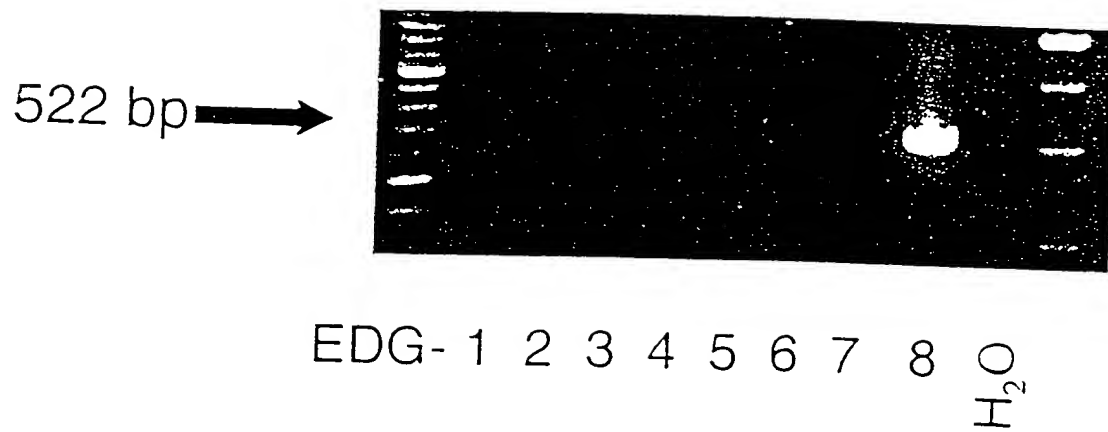
Fig. 6A
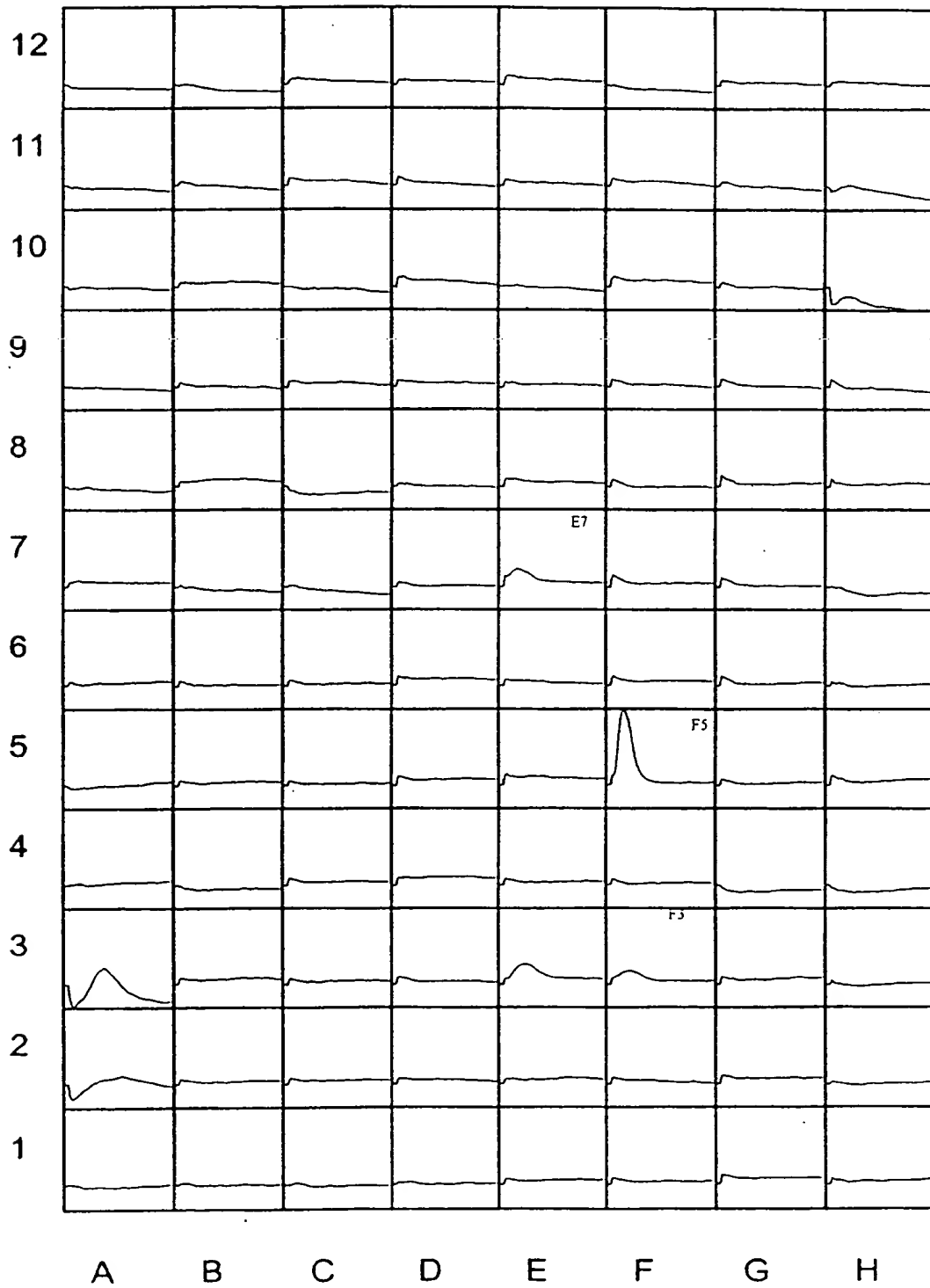
qi5 background

Fig. 6B

rEDG8
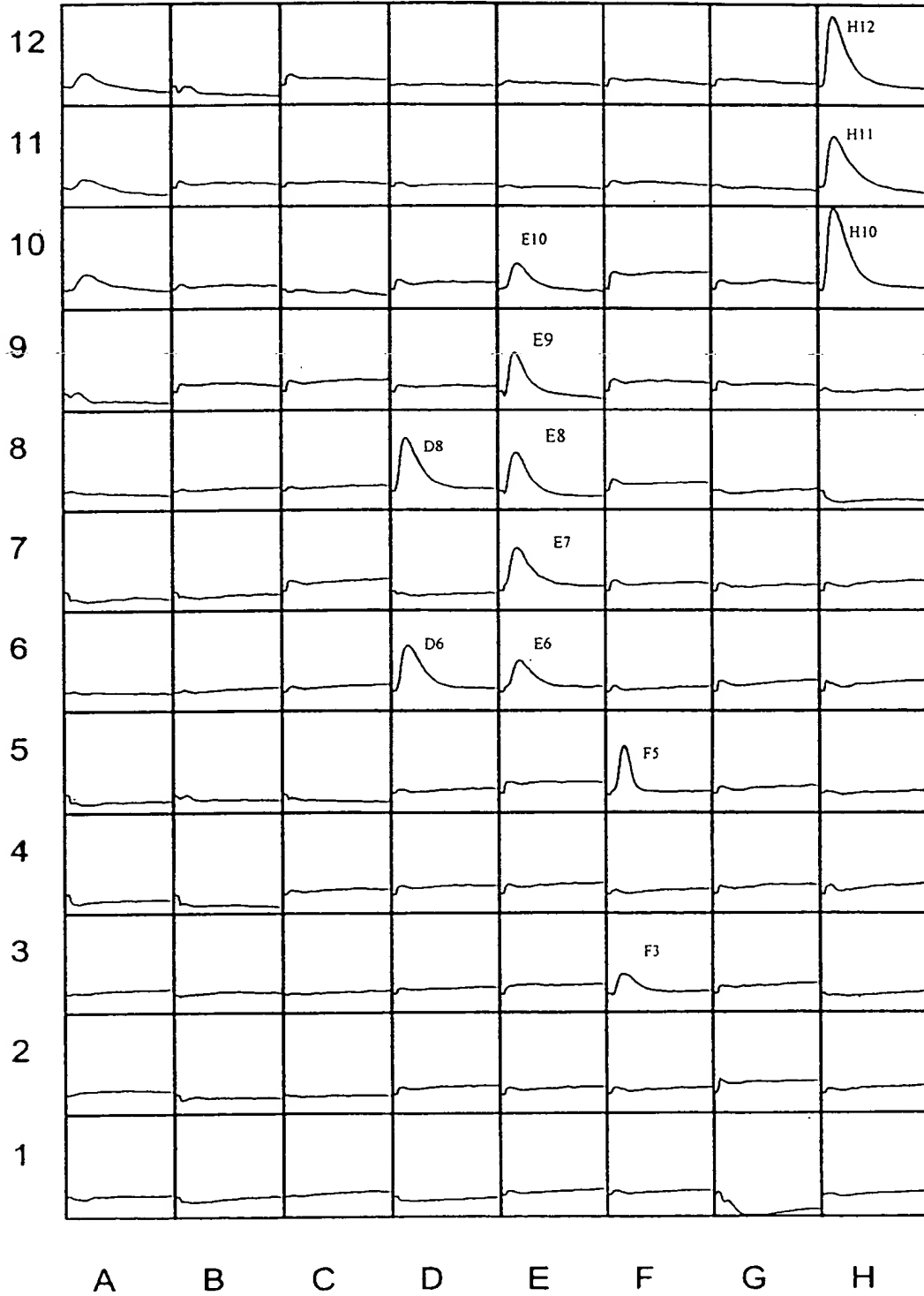
Fig.6C

Fluorescence Change counts

Wells	Lipid	background	rEDG8	stand. response
H10-H12	1µM S1P	0	5196	5196
F5	1µM LPA	5893	4327	-1566
F3	1µM cPAF	1017	1570	553
E10	1µM EPA PAF	0	1354	1354
E9	1µM AA PAF	0	3121	3121
E8	1µM Enantio PAF	0	3883	3883
E7	1µM paf C18:1	1256	3765	2509
E6	1µM Lyso PAF	0	2421	2421
D8	1µM dhS1P	0	5144	5144
D6	1µM S1P	0	3672	3672

Fig. 7A

qi5 background in HEK

Fig. 7B
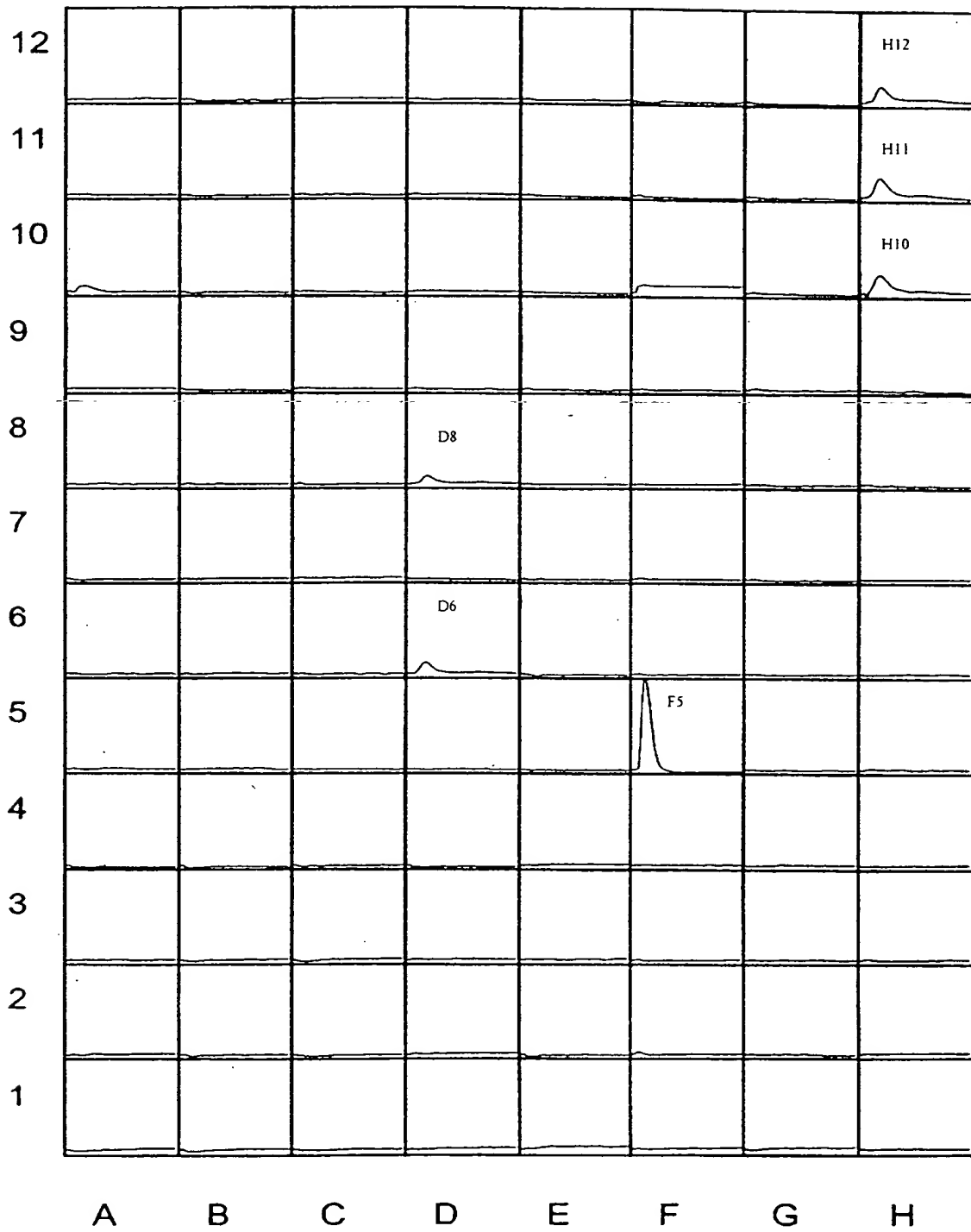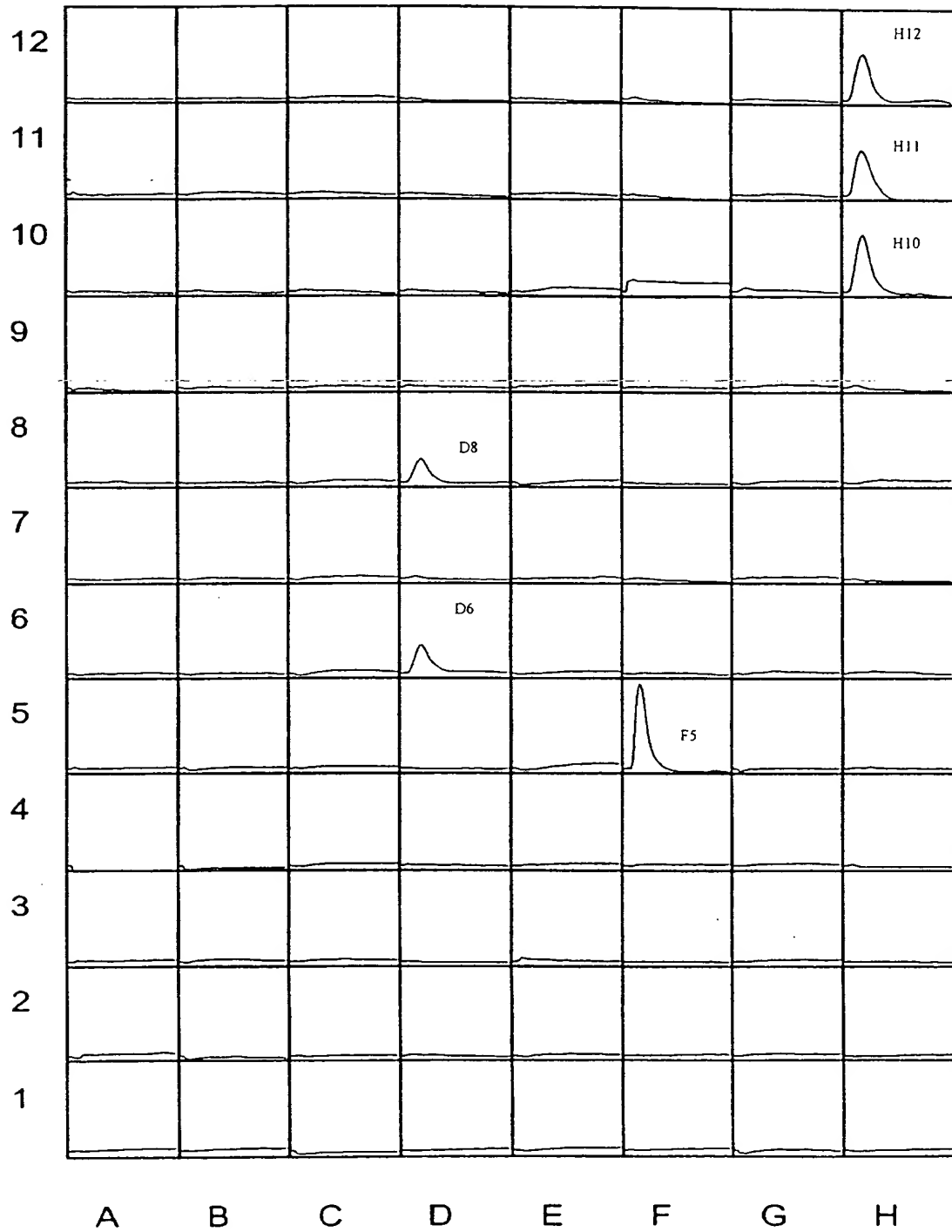
hEDG8

Fluorescence change counts

Wells	Lipid	background	hEDG8	stand. response
H10-H12	1μM S1P	3696	9493	5797
F5	1μM LPA	18004	16333	-1671
D8	1μM dhS1P	1683	4522	2839
D6	1μM S1P	2273	5605	3332

Fig. 7C

FIG 8
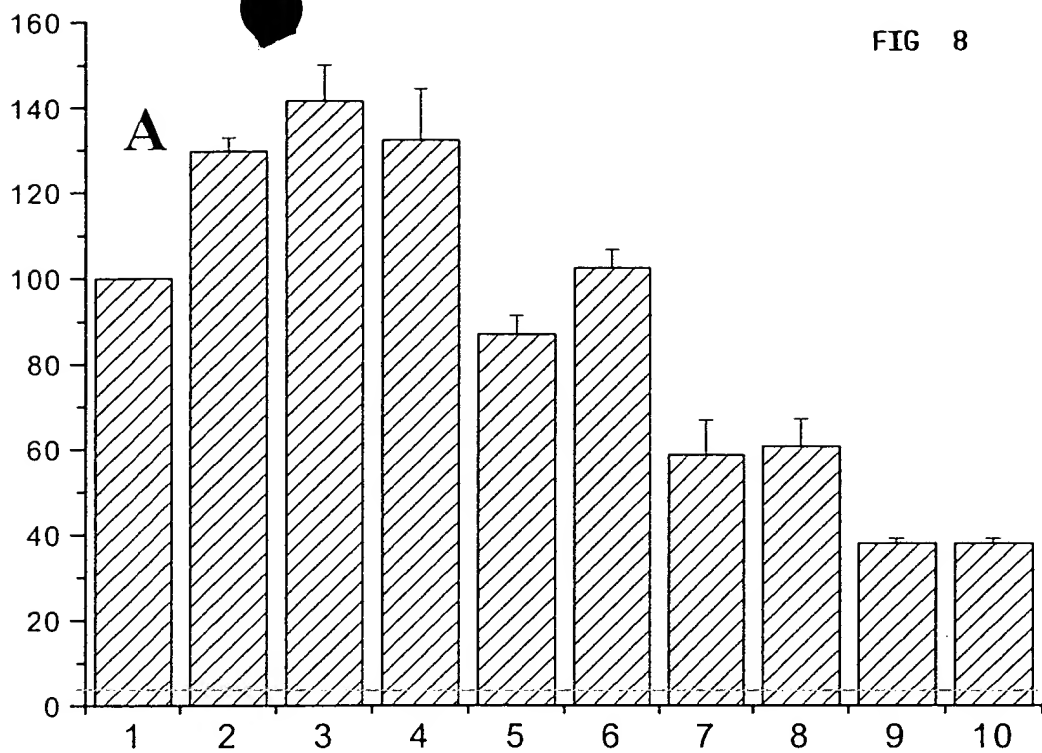
1)S1P 2)Leukotrien B4 3)2 DHLA PAF 4)C$_2$Dihydroceramide
5)15(S)-HEDE 6)PAF C16 7)16,16-Dimethyl PGE$_2$
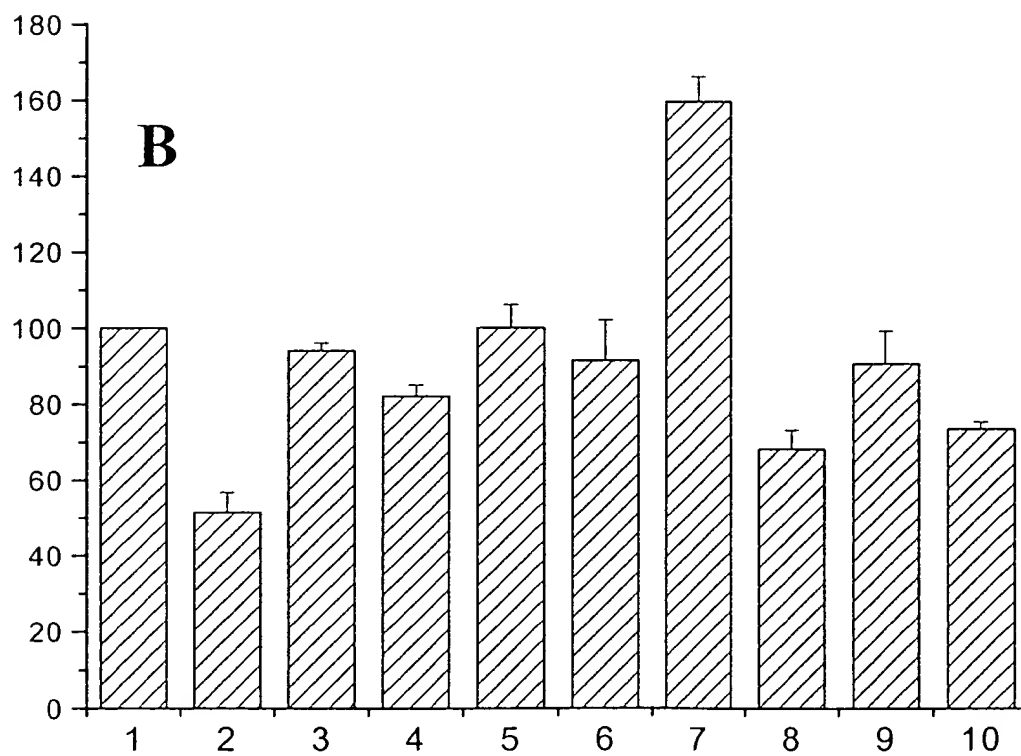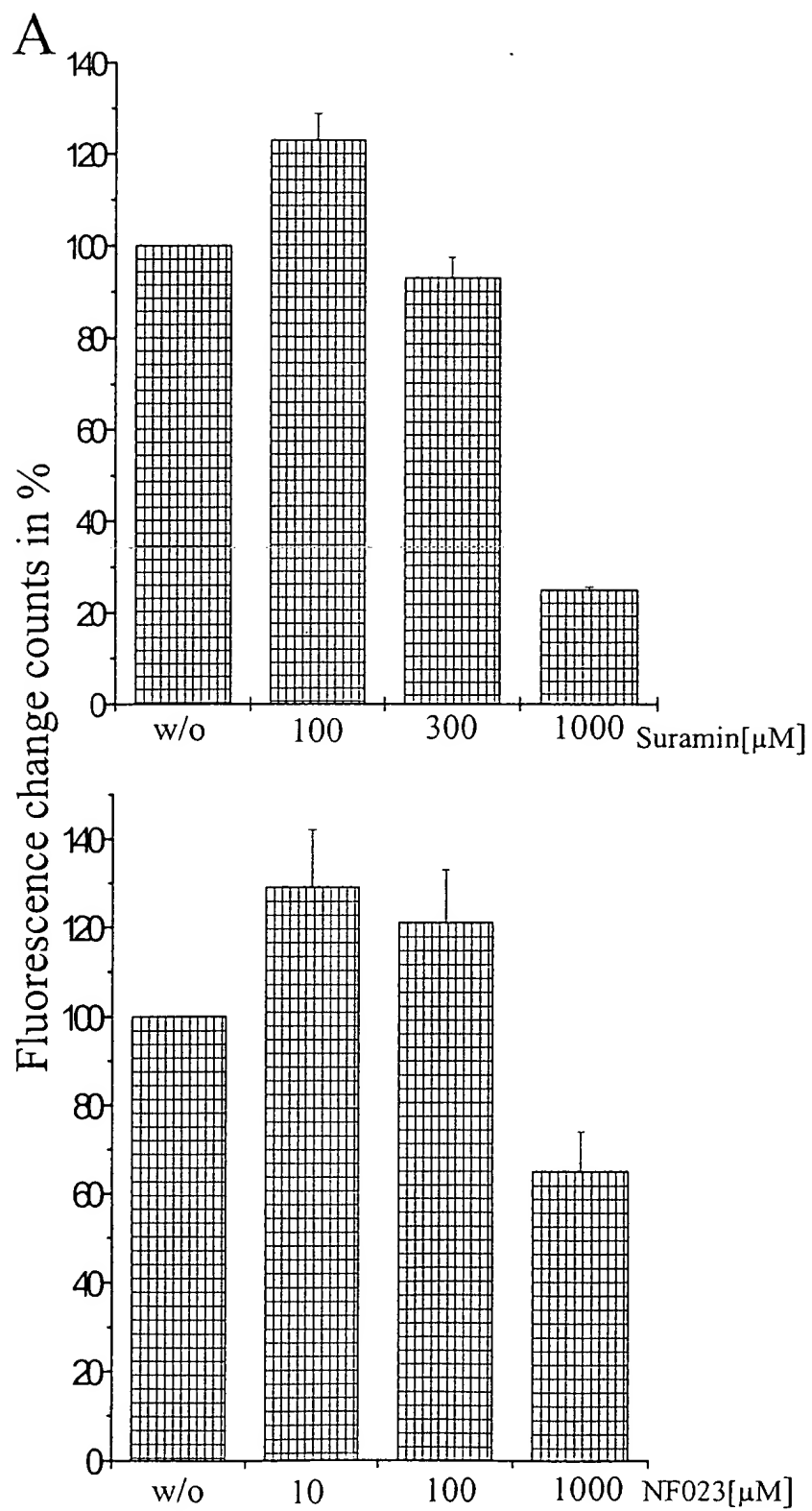8)12(R)-HETE 9)8-Epi-PGF$_{2\alpha}$ 10)Leukotoxin A

% S1P response

FIG 9A

FIG 9B

B Fluorescence change counts in %